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Role of Dynamic Contrast Enhanced MRI in Staging of Bladder Carcinoma

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Abstract:
Objective: *To evaluate the role of contrast enhanced MRI in local staging of bladder cancer and to determine organ confined versus non organ confined disease.*
Patients and methods: *During the study period; from January, 2012 to March, 2014., a total number of 59 cases of histopathology proved urinary bladder cancer were referred from urology department of Al- Hussein University Hospital, for MRI scanning aiming for T-staging of bladder cancer. Both T1 and T2-wieghtedturbo spin echo images were obtained, followed by non-contrast enhanced T1- spoiled gradient weighted image, then fast dynamic gadolinium enhanced T1- spoiled gradient weighted imaging. Contrast enhanced studies were performed with intravenous administration of gadopentetatedimeglumine (Gd-DTPA) (Magnevist) (0.1mmol/kg) followed immediately by 20 ml of IV saline flush injection. Enhanced images were initiated 10 seconds after the start of contrast injection and images were repeatedly acquired four times each 16 seconds at the same sections.*
Results: *The final pathologic staging revealed 23 patients with stage T1, 10 patients with stage T2, 18 patients with stage T3, and 8 patients with stage T4. The MRI dynamic contrast enhanced study shows correct results in 49 cases of 59 patients 83.1%, over-staged in 7 cases of 59 patients 11.8 %, under-staged were 3 cases of 59 patients 5.1 % , sensitivity, specificity, PPV, NPV and accuracy were 81.46%, 94.53%, 79.59%, 94.25% and 91.53%, respectively.*
Conclusion: *We conclude from this study that;fast dynamic gadolinium enhanced MRI images appear to provide useful information for evaluating T-stage in patients with bladder cancer with 91.53% staging accuracy for fast dynamic gadolinium enhanced T1WI. It is particularly useful for differentiating T1-stage or lower tumors from T2-stage or higher tumors. So, contrast enhanced MRI images could be a useful adjunct to preoperative evaluation.*
Key words: *Carcinoma, Urinary bladder, MRI*

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I. Introduction

Urinarybladder cancer is considered one of the most common malignancies worldwide with an incidence of 18.5 per 100,000 males and 5.7 per 100,000 females and approximately 25% of newly diagnosed bladder carcinoma patients present with aggressive muscle-invasive disease (1).

In Egypt, bladder cancer has been the most common male cancer during the past 50 years, representing 16.2% of male cancers, due to the etiological relationship to endemic urinary schistosomiasis. In Egyptian females, it is the 6^{th} most common cancer after breast cancer, non- Hodgkin lymphoma, ovarian cancer, leukemia and colorectal cancer, with its frequency was 4.0%, by far exceeded by breast cancer (37.6% of female malignancies. For both sexes together, the frequency of bladder cancer was 10.1%, nearly the same as non-Hodgkin lymphoma (10.5%) and next in frequency to breast cancer (2).

The decision for the optimal treatment strategy is mainly based on results of imaging. Therefore accurate pre-treatment staging of these patients is of major importance (3).Standard treatment for muscle-invasive bladder carcinoma is radical cystectomy with pelvic lymph node dissection (4).

In patients treated with curative-intended radical cystectomy and pelvic lymph node dissection there is a 40% difference in three year cancer specific survival (91.4 ± 1.7% versus 50.9 ± 3.5%) between those with organ-confined bladder carcinoma and those with a cancer infiltrating perivesical fatty tissue or metastatic lymph nodes (5).

Especially in cases of locally advanced disease or high risk disease for development of metastases platinum-basedneoadjuvant chemotherapyregimens have been shown to improve patient cure rates while palliative treatment is advocated for metastatic disease (6, 7).

MRI is the most promising imaging for staging of cancer bladder. It offers several advantages such as, multiplaner imaging with better detection of tumors, better tissue characterization, superiority in evaluation of prostatic and seminal vesicles invasion in addition to better differentiation post biopsy tissue changes and tumor itself(8).

II. Patients and methods

Prospective study was conducted at MRI unit of radiology department, Al- Hussein University Hospital at the period from January, 2012 to March, 2014. During the study period a total number of 59 cases of histopathology proved urinary bladder cancer were referred from urology department of Al- Hussein University Hospital, for MRI scanning aiming for T-staging of bladder cancer.

In all patients of the study the diagnosis and initial staging of bladder cancers were made by cystoscopy and transurethral resection of the tumor with deep muscle biopsy performed at the base of the tumor. All patients with invasive cancer underwent radical cystectomy and pelvic lymphadenectomy, the extent of bladder tumor was assessed by pathological evaluation of resected bladder and peri-vesical tissues as well as assess of the infiltration of adjacent peri-vesical organ in relation to the tumor and pelvic lymph nodes.

MRI Examination:

All MRI scans were performed at 1.5 Tesla, superconducting magnet, magnetom vision VB 31A (Siemens medical systems, Erlangen, Germany, 1996).

All patients included in the study are found to be free ofdistant metastasis before they were referred for MRI. Theirworkup for distant metastasis included chest X-rays, abdominal sonogram, CT abdomen and bone scanning if required.

MRI technique:

The patient lies supine, feet first on the scanner table, with the median sagittal plane perpendicular to the center of the table. Using the scanner alignment light the external reference point is obtained at the level of the anterior superior iliac spines. From this position the patient is moved to the isocenter of the magnet.

Body coil was used in all patients**.**

An Initial midline sagittal localizer is performed to include the lower abdomen and pelvis. Using this image a series of variable oriented different MRI pulse sequences are obtained.

Both T1 and T2-wieghtedturbo spin echo images are obtained, followed by non-contrast enhanced T1-spoiled gradient weighted image, then fast dynamic gadolinium enhanced T1- spoiled gradient weighted imaging according to the parameters reported in table **(1).**

T2-weighted MR Imaging was performed in axial, sagittal, and coronal planes. An axial T1-weighted image was performed in all cases with additional sagittal or coronal images performed according to the tumor orientation, reviewed on T2-wieghtedimages.

Contrast enhanced studies were performed with intravenous administration of gadopentetatedimeglumine (Gd-DTPA) (Magnevist) (0.1mmol/kg) followed immediately by 20 ml of IV saline flush injection.

Enhanced images were initiated 10 seconds after the start of contrast injection and images were repeatedly acquired four times each 16 seconds at the same sections. The total imaging time for the dynamic sequences is about 64 seconds. Late gadolinium enhanced T1-Wieghted imaging was performed 5 minutes after the dynamic imaging with the same parameters of the previously used conventional T1-Weighted sequence.

Parameters	**Pulse sequences**		
	T1WI	**T2WI**	**Dynamic T1WI**
Repeation time(TR)	800 msec	4000 msec	142 msec
Echo time (TE)	14 msec	120 msec	12 msec
Matrix	256x192	256x192	256 x192
Field of view (FOV)	375 mm	200 mm	375 mm
Slice thickness	5mm	3 mm	5 mm
Inter-slice gap	1 mm	1mm	1 mm
Aqusition time	3:50	3	0.16
Flip angle	-	-	70

Table (1): Study standard MR Pulse sequences parameters.

Diagnostic MRI Criteria

MR images were interpreted without prior knowledge of the final staging obtained at transurethral resection, or cystectomy.

The MRI images were evaluated based mainly on T2-weihgted images and dynamic contrast enhanced T1-weighted images criteria described in deferent previous studies like (9, 10, and 11). T1-weighted images were used to help in differentiate of organ confined from non-organ confined tumors.

On T2-weighted images, the normal bladder wall was identified as a hypointense line outlining the bladder lumen (12, 13). On dynamic contrast-enhanced MR images, bladder tumors, mucosa, and submucosa (lamina propria) enhanced early, but the muscle layer maintained its hypointensity(14). An intact, hypointense line (muscle layer) at the base of the tumor was classified as stage T1; an irregular inner margin of hypointense line, stage T2a. a disrupted hypointense line without perivesical fat infiltration, stage T2b; a lesion with an irregular, shaggy outer border and streaky areas of the same signal intensity of the tumor in perivesical fat, stage T3b; and a lesion extending into an adjacent organ or abdominal and pelvic side walls with the same signal intensity of the primary tumor, stage T4a or T4b, respectively (15). Lymph nodes were considered abnormal if the long axis was 10 mm or more (15). All patients included in the study are found to be free ofdistant metastasis before they were referred for MRI. Theirworkup for distant metastasis included chest X-rays, abdominal sonogram, CT abdomen and bone scanning if required.Pathologic staging conformed to theupdated TNM system of the International Union Against Cancer (table 2).

Statistical analysis.

The collected data were organized, tabulated and statistically analyzed, using Statistical Package for Social Science (SPSS) version 19 (SPSS Inc, Chicago, USA), running on IBM compatible computer with Microsoft ® Windows 7 Operating System. Mean, frequency and percentage were used as descriptive, sensitivity, specificity, positive predictive value ,negative predictive value and accuracy were used as measurements of validity for MRI tumor staging regarding the histopathological results.

Primary tumor (T)		
CIS	Carcinoma in situ.	
Ta	Noninvasive papillary tumor.	
T1	Tumor invades the lamina propria, but not beyond.	
T2	T2a	Tumor invade deep muscle (inner half).
	T2b	Tumor invade superficial muscle (outer half)
T3	T3a	Tumors extend microscopically into perivesical fat.
	T3b	Tumors extend macroscopically into perivesical fat.
T4	T4a	Tumor invades prostate, vagina or uterus.
	T4b	Tumor invades pelvis side wall or abdominal wall.
Regional lymph nodes		
NX	Regional lymph nodes status is unknown.	
N0	No regional lymph nodes metastasis	
N1	Metastasis in a single lymph node 2 cm or less in greatest dimension	
N2	Metastasis in a single lymph node more than 2 cm but less than or equal 5 cm in greatest dimension, or multiple lymph node, none more than 5 cm in greatest dimensio	
N3	Metastasis in a lymph nodes more than 5 cm	
Distant metastases (M)		
MX	Distant metastases cannot be assessed	
MO	No distant metastases	
M1	Distant metastases	

Table (2) TNM staging of bladder carcinoma

III. Results

Patient's sex and age:

59 patients were included in this study, 54 males (91.5%) and 5 females (8.5%) with their age ranged from 43 to 76 years old. The commonest age group encountered in the study was the age group (51-60) years(37.3%).

MRI findings:

Non enhanced T1WI:

In all patients, the urinary bladder tumor appears either as focal mural thickening or mural based endoluminal mass, which has intermediate signal intensity equal to muscle, that the depth of tumor infiltration into the bladder wall cannot be assessed. The interface between the bladder wall and peri-vesical fat was observed for assessment of tumors infiltration into the peri-vesical fat or adjacent organs. On non-enhanced T1-weighted images the tumor was classified into organ confined (T2-stage or less) and non-organ confined (T3-stage or more)**.**

T2WI:

On T2-wieghted images the tumor has intermediate signal intensity, higher than bladder wall, that the depth of tumor infiltration into the bladder wall can be assessed. On T2WI the study has revealed 22 patients with stage T1, 10 patients with stage T2, 20 patients with stage T3, and 7 patients with stage T4.

Gadolinium enhanced fast dynamic T1WI:

On fast dynamic contrast enhanced MRI images, all tumors had increased enhancement compared with uninvolved bladder. The bladder tumor, mucosa and submucosa enhanced early but the muscle layer maintained its hypo-intensity. Gadolinium enhanced T1WI revealed 23 patients with stage T1, 8 patients with stage T2, 18 patients with stage T3, and 10 patients with stage T4.

The final pathologic result and staging:

Urinary bladder carcinomas were pathologically proven in all patient of the study by deep muscle biopsy performed at the base of the tumor during cystoscopy and transurethral resection of the tumor. Noninvasive bladder cancer was proved in 23 patients, and invasive bladder cancer was proved in 36 patients. All patients with invasive cancer underwent radical cystectomy and the extent of bladder tumor was assessed by pathological evaluation of resected bladder and peri-vesical tissues as well as assesses of the infiltration of adjacent peri-vesical organ and excised pelvic lymph nodes.

Transitional cell carcinoma was encountered in 34 of 59 cases (57.63 %), squamous cell carcinoma was encountered in 21 patients (35.59 %), mixed transitional and squamous cell carcinoma was encountered in 3 cases (5.1%) and adenocarcinoma was encountered in one patient of 59 cases (1.69 %).

The final pathologic staging revealed 23 patients with stage T1, 10 patients with stage T2, 18 patients with stage T3, and 8 patients with stage T4.

The tumor were staged correctly in 49 cases of 59 patients 83.1%, overstaged in 7 cases of 59 patients 11.8 %, under stage were 3 cases of 59 patients 5.1 % , sensitivity, specificity, PPV, NPV and accuracy were 81.46%, 94.53%, 79.59%, 94.25% and 91.53%.

MRI	**Histological stage**				
	T1	T2	T3	T4	Total
T1	20	3	0	0	23
T2	3	5	0	0	8
T3	0	2	16	0	18
T4	0	0	2	8	10
Total	23	10	18	8	59

Table (3): Staging results of Gadolinium Enhanced MRI.

MRI		**Pathology stage**			**Sens.**	**Spec.**	**PPV**	**NPV**	**Accuracy**
		Positive	**Negative**	**Total**					
T1	**Positive**	20	3	23	**86.96**	**92.31**	**86.96**	**91.67**	**89.83**
	Negative	3	33	36					
	Total	23	36	59					
T2	**Positive**	5	3	8	**50**	**94.23**	**62.5**	**90.20**	**86.44**
	Negative	5	46	51					
	Total	10	49	59					
T3	**Positive**	16	2	18	**88.89**	**95.35**	**88.89**	**95.12**	**93.22**
	Negative	2	39	41					

	Total	18	41	59					
T4	**Positive**	8	2	10	**100**	**96.23**	**80**	**100**	**96.61**
	Negative	0	49	49					
	Total	8	51	59					
Mean					**81.46**	**94.53**	**79.59**	**94.25**	**91.53**

Table (4): Sensitivity, Specificity, PPV, NPV and accuracy of Gadolinium Enhanced MRI

Superficial versus invasive tumors:

Staging accuracy was evaluated by another way to reflect clinical utility. We evaluate the ability MRI to distinguish between the superficial and invasive tumors.

On gadolinium enhancement T1WI, 53 tumor were staged correctly(89.83%), 3 were overstaged (5.08%), 3 were understaged (5.08%), yielding an overall sensitivity were 78.26%, specificity 88.89%, PPV 81.82% , NPPV were 86.49% and accuracy were 89.83%.

MRI		**Histological stage**		
		Superficial	**Invasive**	**Total**
MRI stage	**Superficial**	20	3	23
	Invasive	3	33	36
	Total	23	36	59

Sens.	**Spec.**	**PPV**	**NPV**	**Accuracy**
86.96	91.67	86.96	91.67	89.83

Table (5): Accuracy of gadolinium enhanced MRI indifferentiating superficial from invasive tumor

Organ confined versus non-organ confined:

Non enhanced T1WI revealed 38 patients with organ confined and 21 patients non-organ confined. T2WI revealed 32 patients with organ confined and 27 patients with non-organ confined. Gadolinium enhanced T1WI revealed 31 patients organ confined and 28 patients with non-organ confined tumor. The final pathologic staging revealed 33 patients with organ confined and 26 patients non-organ confined tumors.

Lymph node staging

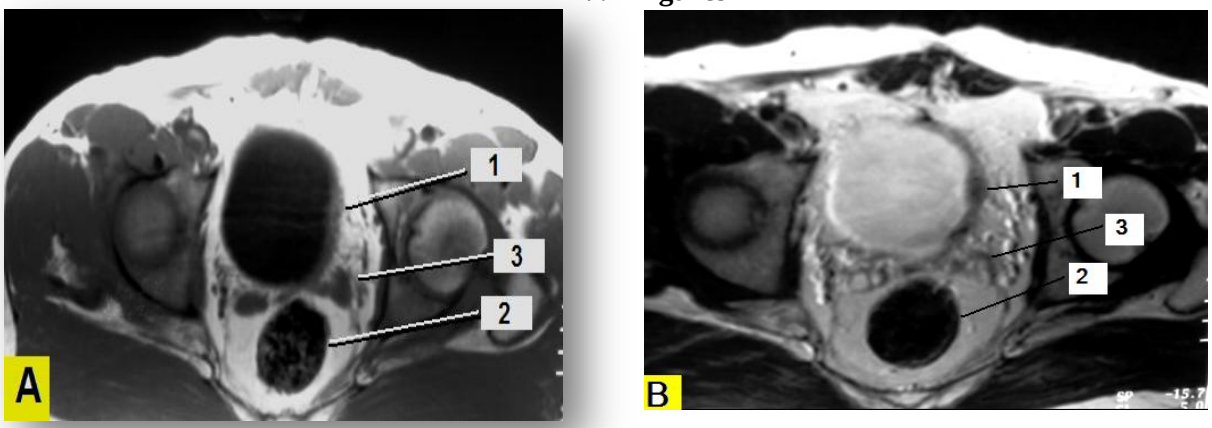
MRI images revealed 7 patients of 59 patient with enlarged pelvic lymph nodes with their diameter exceeding 10 mm and 52 patients who were free of lymph node enlargement. All patients with enlarged lymph nodes were of invasive cancer bladder (T2-T4-stage). Of these 7 patients of MRI detected enlarged lymph nodes, 6 patients proved to be neoplastic lymph nodes and 1 false positive case which revealed inflammatory changes on final pathologic staging. The final pathologic staging revealed 8 patients with neoplastic lymph node involvement. That neoplastic lymph nodes were correctly detected in 6 patients of 7 MRI detected enlarged lymph nodes compared to 8 patients with histopathology proved neoplastic lymph nodes with sensitivity, specificity, PPV, NPV and accuracy were 75 % , 98%., 85%, 96% and 94.9%

Lymph node		**Histological stage**		
		N0	**N1-N2**	**Total**
MRI stage	**N0**	50	2	52
	N1 –N2	1	6	7
	Total	51	8	59

Sens.	**Spec.**	**PPV**	**NPV**	**Accuracy**
75	**98**	**85.7**	**96**	**94.9**

Table (6) : MRI lymph node staging results.

IV. Figures



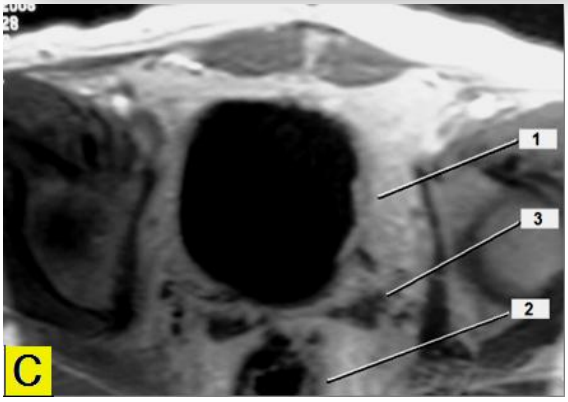


Fig- (1).Grad III TCC. Urinary bladder left lateral wall thickening lesion, shows isointense T1 signal to muscle (Image A), heterogeneous intermediate T2WI signal (Image B), and marked T1 post-contrast enhancement(Image c),. The normal peripheral hypo-intense muscle layer cannot be visualized on T2WI , but on T1 post-contrast images it can be seen as irregular, partially attenuated continuous hypo-intense line surrounds the outer bladder contour at the site of the lesion with no extra-vesical extension. No pelvic lymph-adenopathy.1:Bladder mass. 2: Rectum. 3:Seminal vesicle.

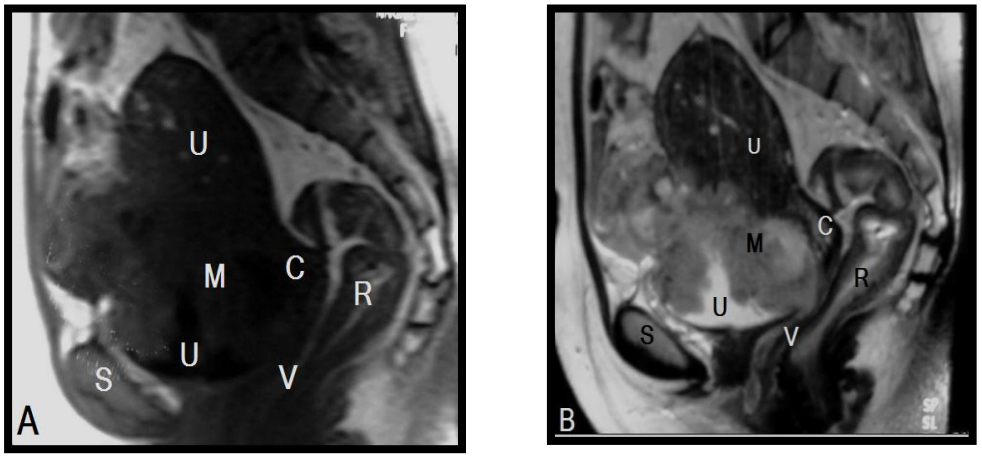
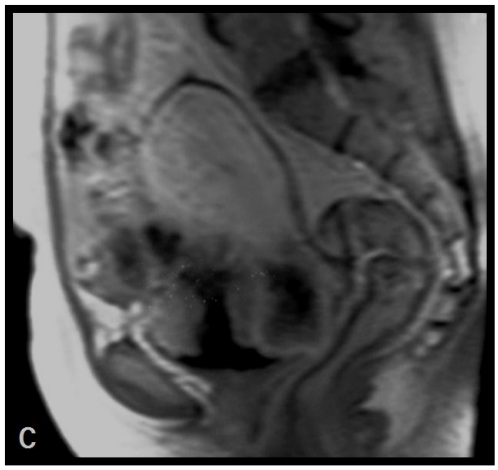


Fig (2).(T4.b-stage). Large exophytic urinary bladder mass lesion is seen involving the anterior wall, dome and posterior wall of bladder. The mass is disrupting the urinary bladder muscle coat, infiltrating the ventral uterine body and cervix as well as anterior vaginal wall. The mass shows T1WI signal isointense to muscle (Image A), heterogeneous increased T2WI signal (Image B), and marked T1 post contrast enhancement (Image C). A : T1WI. B: T2WI C: T1-post contrast. U=Uterus C= Uterine cervix V=Vagina R=Rectum M= Mass U= Urinary bladder. S= Symphysis pubis



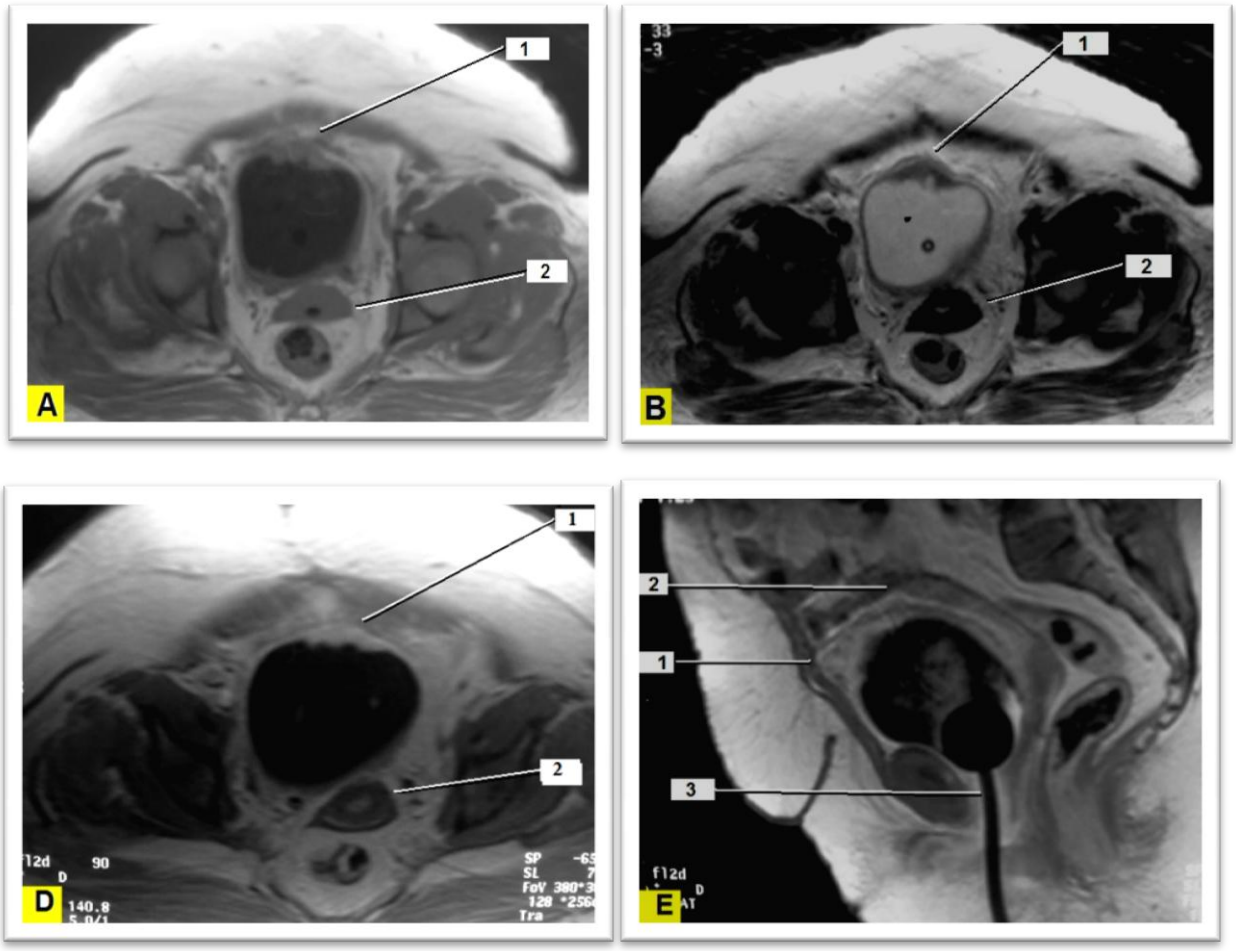


Fig (3).(T1-stage).Urinary bladder dome and anterior wall mass lesion of T1WI signal isointense to muscle (Image A), heterogeneous increased T2WI signal (Image B and C), and marked T1 post-contrast enhancement (Image D and E). The normal hypo-intense outer muscle layer overlying the mass is disrupted on T2WI, but appears intact and can be traced on T1 post-contrast image. No extra-vesicle extension and peri-vesical fat is clear. No pelvic lymph-adenopathy.A : T1WI. B: T2WI. C: T1-post contrast. 1: Bladder mass. 2: Uterus. 3: Folley's catheter.

V. Discussion

Urinary bladder cancer is a common disease worldwide with its incidence varies significantly between geographical regions and countries(16).In Egypt, bladder cancer has been the most common male cancer during the past 50 years, representing 16.2 % of male cancers. In Egyptian females, it is the 6th most common cancer after breast cancer, non- Hodgkin lymphoma, ovarian cancer, leukemia and colorectal cancer (2).

Approximately 90 % of all bladder cancers are transitional cell carcinomas (TCC) in western countries, mainly related to smoking risk factor(16). Egypt had different histological pattern than other countries with high incidence of squamous cell carcinoma (SCC) related to endemic schistosomiasis(17)**.** There are multiple studies reported significant changes in the histo-pathological profile of bladder cancer in Egypt over the last few decades due to the effect of successful control measures against endemic schistosomiasis (17).

In our study transitional cell carcinoma was encountered in 34 of 59 cases (57.63 %), squamous cell carcinoma was encountered in 21 patients (35.59 %), mixed transitional and squamous cell carcinoma were encountered in 3 cases (5.1%) and adenocarcinoma were encountered in one patient of 59 cases (1.69 %).

These results are agree with previously mentioned multiple studies which reported the increase in frequency of TCC and decrease in frequency of SCC relative to previous early reports, which indicate a transition phase from the schistosomiasis associated bladder cancer to the western pattern of bladder cancer, which is mainly related to smoking risk factor.

The correct staging of bladder cancer at time of presentation is a significant prognostic value and essential in planning therapy. The treatment and prognosis of carcinoma of urinary bladder are largely determined by the depth of tumor infiltration and extent of metastases (18)

Various imaging methods including, ultrasonography (US), CT and MRI have been introduced to improve the staging accuracy of bladder cancer.

USis easily available, cost effective, non-ionizing and non-invasive technique, requiring no special preparation, providing images of both the upper and lower urinary tract(19).Despite the remarkable improvements in the diagnostic accuracy, some of the pitfalls of US for evaluation of the bladder still remain. Smaller lesions (smaller than 0.5 cm) and lesions located in the dome or bladder neck are more difficult to visualize sonographically. Tumor configuration is also an important factor; plaque-like lesions are almost certainly harder to detect than polypoid ones. In addition, accuracy in the detection of lymph node metastases remains very low(20)**.**

The current standard pre-operative imaging modality represents contrast-enhanced computed tomography (CT). However, in up to 40% of cases, CT underestimates the disease(5). It has been reported that CT can only marginally differentiate between tumor stages Ta to T3a and even in cases with macroscopic invasion of perivesical fatty tissue, accuracy rates rangefrom 55–92%(4). In addition, regenerative and inflammatory postoperative tissue alterations after previous transurethral resection of the bladder carcinoma further impair exact local T-staging. The sensitivity for detection of lymph node metastases (48–87%) is also disappointing.

MRI Imaging of the urinary bladder has been investigated by many studies and most of the published reports have concentrated on the ability of MR imaging to diagnose and stage primary urinary bladder carcinoma and benefit of contrast enhanced images in improvement of staging accuracy.

In this study the ability of MRI to differentiate local tumor stage on stage by stage basis was assessed and compared to the confirmed pathologic staging data obtained from TUR deep muscle biopsy performed at the base of the tumor and by pathologic evaluation of resected bladder and peri-vesical tissues after total cystectomy.

Our staging accuracy for fast dynamic Gd-T1WI was 91.53%, which is concurs with existing resultsin the literature by(21), who reported an accuracy of 92% with contrast administration. Our staging accuracy for fast dynamic Gd-T1WI were higher than the results reported by(22, 23, 24) which revealed accuracy 86%, 62% and 79% respectively , but lower than that reported in the study by (25) which revealed 95 % accuracy.

Our study is agreed with all previously mentioned studies in that; the overall accuracy in tumor staging improves after use of gadolinium enhanced MR imaging. For examples, in(22)and (24), the overall accuracy improved from 77.7 % to 86% and from 67% to 79% respectively after use of gadolinium enhanced MR imaging. In our study overall accuracy improved from 85.6 % to 91.53% after use of gadolinium enhanced MR imaging

Our staging accuracy for T2WI in assessing superficial versus invasive disease was 84**.**75% , which increased to 89.83%after contrast administration. This accuracy results are close to the results reported by (23**),** who demonstrated overall staging accuracies of 85% for T2WI and Gd-T1WI in differentiating superficial from muscle invasive tumors and higher than that reported by (21)**,** who reported that muscular infiltration is correctly staged in 54.5 % by unenhanced MR imaging, the accuracy increase after use of dynamic enhanced imaging up to 59%.

Our study reported 11.8 % for contrast enhanced T1WI when evaluating T-stage. This is contrary to the findings of the study by (26), which used a 0.5-T MR scanner without contrast administration and reported that, the most common staging error was underestimation in (33%) of the patients of the study. (23)reported that, overstaging was the most common error in (32%) of patient of the study when evaluating T stage.

Lymph nodes

In our study nodal assessment with MR imaging which relies on nodal size shows sensitivity, specificity and accuracy in detecting lymph node involvement were 75%, 98% and 94.9% respectively. These data is close to the result of (23), which reported sensitivity, specificity and accuracy 78%, 98% and 96%, respectively in detecting lymph node involvement. It is also close to the result demonstrated by(27)which reported sensitivity, specificity and accuracy 76%, 99% and 92% respectively.

We conclude from this study that fast dynamic gadolinium enhanced MRI images appear to provide useful information for evaluating T-stage in patients with bladder cancer with 91.53% staging accuracy for fast dynamic gadolinium enhanced T1WI. It is particularly useful for differentiating T1-stage or lower tumors from T2-stage or higher tumors, with over stage error in 11.8% and under stage in 5.1% respectively for contrast enhanced MRI images. So, contrast enhanced MRI images could be a useful adjunct to preoperative evaluation.

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